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VON SEGGERN *et al.*  
AMENDMENT AFTER FINAL**

**REMARKS**

A check for the requisite fee for a three month extension of time and a Notice of Appeal accompanies this response. Any fees that may be due in connection with filing this paper or with this application may be charged to Deposit Account No. **06-1050**. If a Petition for extension of time is needed, this paper is to be considered such Petition.

The Examiner is thanked for her courtesy in granting interviews and reviewing the proposed amended claims. The amendments provided herein are in accord with the proposed amendments and the interviews with the Examiner.

Claims 1, 2, 4-12, 14-23, 41, 47, 69 and 95-103, are presently pending in this application. Claim 13 is cancelled herein. Claims 1 and 2 are amended as suggested by the Examiner in the interview of November 23, to clarify that the limitations on the TPL exons apply to clauses (a) and (b) of the claims. Claim 6, although allowed, is similarly amended for consistency of language.

Claims 9 and 100 are rewritten as independent claims directed to nucleic acid molecules contained in particular species of plasmids (pDV60, pDV67, pDV69, pDV80, pDV90 for Claim 9 and pCLF for Claim 100). The amendment finds basis in the specification, for example, at page 6, lines 7-23, page 37, lines 3-9, in Example 1B, beginning at page 65, in Example 5, beginning at page 92, Example 6, beginning at page 94, Example 10, beginning at page 107 and Example 11, beginning at page 110. No new matter is added.

Claims 12, 41, 47, 95-97 also are amended herein to include the limitations of allowed Claim 6 or the limitations of Claims 1 or 2 as amended herein (*i.e.*, specifying nucleic acids encoding adenovirus TPL exons from different adenoviruses or non-native order or both and selected from a specified group of TPL exons). Basis for these amendments may be found in Claims 1, 2 and 6 as originally filed and in the specification, for example, at page 28, lines 27-30; page 34, lines 23-25; page 35, lines 26-28; page 36, lines 17-19 and 21-23; and Example 5 at page 93, lines 17-19. Claim 12 also is amended

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herein, as suggested by the Examiner in the interview of December 2, to replace "consists essentially of" with "comprises" and clarify that the TPL leader sequence contains three component exons. Claims 41 and 47 are amended to depend from Claim 95 and render the claim set more concise, as discussed in the interview of December 2. Claims 95-97 also are amended herein for clarity as suggested by the Examiner in the interview of December 2.

Claim 14 is rewritten as an independent claim incorporating all the limitations of the base Claim 12, and Claims 18 and 19, which are species of Claim 14, are amended accordingly to depend from Claim 14. Therefore, Claims 14 and dependent claims 18 and 19 should be allowable as acknowledged by the Examiner (see page 16, Final Office Action). No new matter is added.

The specification is amended to correct an inadvertent error. It is amended to identify the origin of the TPL sequence of plasmid pCLF. The paragraph at page 66, line 13, through page 67, line 5, is amended to replace "adenovirus type 5" with —adenovirus type 2—. The paragraph at page 95, lines 7-13, is amended to replace "Ad5" with —Ad2—. These amendments find basis in Sheay *et al.*, BioTechniques, 15:856-862 (1993), which is incorporated by reference in the application as filed. Plasmid pRD112a, described by Sheay *et al.*, contains TPL sequences from Ad2. As described in the specification, a BgIII fragment from this plasmid was excised and ligated with pcDNA/Fiber to create plasmid pCLF. Thus, the TPL sequences present in pCLF are derived from Ad2 and amendment of the specification accordingly finds basis in the application as originally filed. No new matter has been added to the specification.

It is respectfully submitted that entry of the amendments should place the case into condition for allowance. Claims 5-8 are deemed allowed by the Examiner. Further, for example, as noted above, Claims 1 and 2 are amended to clarify that the limitation that the TPL exons be from different adenoviruses or in non-native order or both applies to (a) and (b). As the Examiner has

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acknowledged (see Final Office Action page 15 and also discussed during the interviews of November 23 and December 2), the prior art does not teach or suggest nucleic acids encoding adenovirus TPL exons from different adenoviruses or non-native order or both, where the TPL exons are selected from the groups specified in these claims. Therefore, it is respectfully submitted that this amendment should place Claims 1-4 and 11 in condition for allowance.

Claims 12, 41, 47, 95-97 also are amended herein, as suggested by the Examiner in the interview of December 2, to include the limitations of allowed Claim 6 or the limitations of Claims 1 or 2 as amended herein (*i.e.*, specifying nucleic acids encoding adenovirus TPL exons from different adenoviruses or non-native order or both and selected from a specified group of TPL exons); therefore, these claims and claims dependent thereon also should be allowable.

Further, in order to place Claims 14 and 19 into condition for allowance (see Final Office Action page 16) as suggested by the Examiner, Claim 14 is rewritten as an independent claim incorporating all the limitations of the base Claim 12; therefore, Claim 14 and claims dependent thereon, including Claim 19 as amended herein, should be allowable. Claim 13 is cancelled herein, thereby rendering its rejection moot. The rejection of Claims 9, 18, and 100-103 as allegedly lacking enablement also has been addressed as suggested by the Examiner in the interviews of November 23 and December 2. Accordingly, it is respectfully submitted that the claims as amended herein are allowable and should place the application in condition for allowance.

**Claims 9, 100, 14, 18 and 19, drawn to particular plasmids and sequences, are patentable over the cited Art**

As amended herein, Claims 9, 14 and 100 are rewritten as independent claim incorporating all limitations of the base claims upon which each depends. None of these claims are rejected as anticipated or obvious over cited art.

With respect to Claim 14, as the Examiner has acknowledged (see page 16 of the Final Office Action), the prior art does not disclose, teach or suggest

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its subject matter and the claim would be allowable if rewritten as an independent claim incorporating all the limitations of the base claim. Therefore, it is respectfully submitted that Claim 14 as amended herein, and Claims 18 and 19 dependent thereon, should be allowable.

With respect to Claims 9 and 100, as stated above, neither of these claims are rejected over cited art. Claim 9 is drawn to an isolated nucleic acid molecule contained in a plasmid selected from the group consisting of plasmids pDV60, pDV67, pDV69, pDV80 and pDV90. Claim 100 is drawn to a nucleic acid molecule contained in the plasmid pCLF. The claims as amended incorporate the limitations of their base claims. Therefore, the claims as amended are free of the art.

Claims 9 and 100 are rejected under 35 U.S.C. §112, first paragraph. This issue was addressed in the interview and is addressed below. As discussed below in addressing the rejection on grounds of lack of enablement, the complete sequences of each of the plasmids that are elements of Claims 9 and 100 are included in the application. The Examiner indicated that pointing out the sequence identifier for each plasmid in the response addresses this rejection. Therefore, pursuant to the interviews of November 23 and December 2, Claims 9 and 100, which are free of the art, should be allowable.

**STATEMENT OF THE SUBSTANCE OF THE INTERVIEWS OF NOVEMBER 23, 2004, AND DECEMBER 2, 2004 WITH THE EXAMINER**

Applicant thanks the Examiner for the courtesy extended in granting interviews to discuss specific issues raised in the Final Office Action of June 2, 2004. Pursuant to the discussion, Applicant further thanks the Examiner for agreeing to consider the instant Amendment after Final that incorporates the Examiner's suggestions provided during the aforementioned interviews.

In the interview of November 23, Applicant discussed the Examiner's rejection of the pending claims 1, 2 and 11 under 35 U.S.C. §102(b) over Logan *et al.* In the Final Office Action, it is alleged that the "sub 360-L1,3" construct

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of Logan *et al.* anticipates a nucleic acid molecule containing two TPL exons in an order not normally found together in nature, including such a molecule operatively linked to an intron containing an RNA processing signal, as set forth in Claims 1 and 2, respectively. Applicant pointed out that Logan *et al.* does not disclose any construct in which the TPL exons that are operatively linked in non-native order are selected from the group consisting of complete TPL exon 1, complete TPL exon 2 and complete TPL exon 3 (for Claim 1 and dependent Claim 11) or the group consisting of complete TPL exon 1, partial TPL exon 1, complete TPL exon 2 and complete TPL exon 3 (for Claim 2). The "sub 360-L1,3" construct of Logan *et al.* contains partial TPL exon 1 operatively linked to partial TPL exon 3.

Upon further review and discussion of Logan *et al.*, the Examiner suggested amendment of the language of Claims 1 and 2 to clarify that the limitations on the TPL exons apply to clauses (a) and (b) of these claims. The Examiner also agreed to reconsider the obviousness rejections (Claims 4, 12, 13, 15-17, 20-23, 41, 47, 69 and 95-97) set forth in the Final Office Action, which cite Logan *et al.* as a primary reference.

With respect to the rejection of Claims 9, 18, 100, 102 and 103 as lacking enablement because the subject matter (plasmids) were not described in the specification in a manner that would allow one of skill in the art to make or use the claimed subject matter, the Examiner agreed to reconsider the rejection if Applicant clearly pointed to passages in the specification that described the complete sequences of each of these plasmids.

At the conclusion of the interview, it was agreed that Applicant would provide an amended claim set in accordance with the above suggestions, for the Examiner's review and consideration. The Examiner reviewed the amended claims and extended Applicant the courtesy of a second interview on December 2, 2004.

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In the interview of December 2, the Examiner indicated that while most of the claims appear allowable if the issues are addressed as was discussed on November 23, she would consider allowance of Claims 12, 41 and 95-97 if they were amended to incorporate the limitations of Claim 1. Applicant explained that these claims, drawn to packaging cell lines and related methods in which the packaging cell lines contain TPL leader sequences and adenoviral structural protein genes stably integrated into the genomes of the cell lines, were not taught or suggested by the cited references, singly or in any combination. The Examiner responded that further searching was necessary to ascertain non-obviousness of the claims on these grounds, and suggested filing the claims as pending in a continuation application. In the interest of advancing the application to allowance, Applicant has amended the claims to incorporate the suggested limitations, and reserves the right to file continuation application(s) directed to the claims as pending.

The Examiner also suggested cancellation of either Claim 41 or Claim 95 cancelled, because they are very similar. Applicant suggested amending Claim 41 to depend from Claim 95, and the Examiner agreed to consider such amendment.

The Examiner also suggested amending several claims for clarity as follows:

Claim 12: replace the language "consisting essentially of" with "comprises"

Claims 95-97: designate one set of "(a)" and "(b)" clauses as "(i)" and "(ii)", to eliminate confusion between the two sets of "(a)" and "(b)" clauses in each of these claims.

It is respectfully submitted that, as discussed below, the instant Amendment after Final is compliant with the Examiner's suggestions as set forth during the interview. It is further submitted that the instant Amendment after Final is fully responsive to the Final Office Action of June 2, 2004, and either

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places the application into condition for allowance, or, alternatively, reduces the number of issues for appeal.

**THE REJECTION OF CLAIMS 41, 47 AND 95-97 UNDER THE JUDICIALLY CREATED DOCTRINE OF OBVIOUSNESS-TYPE DOUBLE PATENTING**

Claims 41, 47 and 95-97 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 57, 58, 60, 65 and 66 of copending U.S. Application Ser. No. 09/795,292. The Office Action alleges that although the claims are not identical, they are not patentably distinct from each other because Claims 41, 47 and 95-97 of the present application allegedly anticipate claims in the copending application that are drawn to methods of producing an adenovirus vector with a cell complementing a fiber gene in a fiberless adenovirus genome with a nucleic acid containing a stably integrated TPL sequence. This rejection is respectfully traversed.

**RELEVANT LAW**

The disclosure of a patent cited in support of a double patenting rejection cannot be used as though it were prior art **even where the disclosure is found in the claims.** Obvious-type double patenting signifies that the difference between first-patented invention and its variant involves only an unpatentable difference, such that grant of the second patent would extend the right of exclusivity conferred by the first patent. Comparison can be made only with what **subject matter is claimed** in the earlier patent, paying careful attention to the rules of claim interpretation to determine what invention a claim defines and not looking to the claim for anything that happens to be mentioned in it as though it were a prior art reference. A fundamental rule of claim construction requires that what is claimed is what is defined by the claims taken as a whole, every claim limitation (each step) is material. General Foods Corp. v. Studiengesellschaft Kohle mbH, 23 USPQ 1839 (Fed. Cir. 1992).

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Obviousness-type double-patenting has not been found in instances in which the claims at issue do not embrace the prior patent compounds and/or the claims in the prior patent do not suggest any modification that would have produced the claimed compounds in the patent or application at issue (see, e.g., Ortho Pharmaceutical Corp v. Smith, 22 USPQ2d 1119 (Fed. Cir. 1992)), in which obvious-type double patenting was not found in an instance in which the claims in the patent at suit were directed to compounds that did not encompass, structurally, the compounds claimed in the prior patents, and the compounds claimed in the prior patents did not suggest a modification of those compounds to produce compounds claimed in the patent at suit.

Thus, obvious-type patenting does not exist if the claims at issue do not encompass the claimed subject matter in the copending application, and, the claims in the copending application do not suggest a modification to produce the claims in the subject application.

**CLAIMS**

**Claims of U.S. Application No. 09/795,292**

Independent Claim 57 recites:

A method for producing an adenovirus vector particle containing a helper-independent fiberless recombinant adenovirus vector genome comprising:

- a) providing a packaging cell line that encodes gene products that complement replication and packaging of said genome;
- b) introducing into said cell line a helper-independent fiberless recombinant adenovirus vector genome that comprises a mutated or deleted fiber gene, wherein packaging of a fiber-containing adenovirus particle requires complementation of the fiber gene to support assembly of the fiber-containing particle;
- c) growing said cell line under conditions for producing particles; and
- d) harvesting an adenovirus vector particle produced by step (c)

Dependent Claim 58 further specifies that the packaging cell line encodes gene products that complement adenovirus fiber protein

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Dependent Claim 60 specifies that the adenovirus packaging cell line contains:

a stably integrated nucleic acid molecule, which comprises an adenovirus tripartite leader (TPL) nucleotide sequence operatively linked to an intron containing a RNA processing signal, said TPL nucleotide sequence comprising (a) first and second different TPL exons or (b) first, second and third different TPL exons, said TPL exons selected from the group consisting of complete TPL exon 1, partial TPL exon 1, complete TPL exon 2 and complete TPL exon 3; an intron containing RNA processing signals;

a promoter; and

a nucleic acid sequence which encodes an adenovirus structural protein, each operatively linked in said nucleic acid molecule such that the structural protein is expressed under the control of said promoter and said TPL sequence, and wherein said TPL sequence consists essentially of a first TPL exon operatively linked to a complete second TPL exon operatively linked to a complete third TPL exon.

Dependent Claim 65 specifies that

said providing of said packaging cell line comprises the step of transfecting a cell with a nucleic acid molecule capable of expressing said adenovirus fiber protein to form said packaging cell line.

Dependent Claim 66, which is pending but withdrawn from consideration as reading on a non-elected species, specifies that:

the nucleic acid molecule is an isolated nucleic acid molecule comprising an adenovirus tripartite leader (TPL) nucleotide sequence operatively linked to an intron containing a RNA processing signal, said TPL nucleotide sequence comprising (a) first and second different TPL exons or (b) first, second and third different TPL exons, said TPL exons selected from the group consisting of complete TPL exon 1, partial TPL exon 1, complete TPL exon 2 and complete TPL exon 3, further comprising a promoter and a nucleic acid sequence which encodes a structural protein, operatively linked such that the structural protein is expressed under the control of said promoter and said TPL sequence, wherein said structural protein is adenovirus fiber protein or a chimeric protein which includes an adenovirus fiber protein tail domain.

None of the above claims teach or suggest TPL constructs containing exons from different adenoviruses or in non-native order, or both.

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**Pending claims in this application**

Claim 95 is directed to a method for producing an adenovirus particle comprising:

1) providing a packaging cell line wherein said packaging cell line comprises:

(i) a stably integrated first nucleic acid molecule operatively linked to a second nucleic acid molecule encoding an adenovirus structural protein, wherein said first nucleic acid molecule comprises the nucleic acid molecule of claim 2; and

ii) said cell line supports the production of a recombinant adenovirus vector genome by complementation of a deficient viral gene in said vector genome, and

2) producing said virus particle.

The nucleic acid molecule of claim 2 is an isolated nucleic acid molecule, comprising: a sequence of nucleotides encoding an adenovirus tripartite leader (TPL) that comprises (a) first and second different TPL exons, wherein the different TPL exons are from different adenoviruses, or in a non-native order or both or (b) first, second and third same or different TPL exons, wherein at least two of the different TPL exons are from different adenoviruses, or in a non-native order or both, said TPL exons in (a) and (b) selected from the group consisting of complete TPL exon 1, partial TPL exon 1, complete TPL exon 2 and complete TPL exon 3, wherein the sequence of nucleotides encoding a TPL is operatively linked to an intron containing an RNA processing signal.

Dependent Claims 41 and 47 specify that the first nucleic acid molecule is operatively linked to a promoter (Claim 41) or the adenovirus structural protein is adenovirus fiber protein.

Claim 96 recites a method for producing an adenovirus particle comprising:

1) providing a packaging cell line wherein said packaging cell line comprises:

(i) a stably integrated nucleic acid molecule, comprising:  
a sequence of nucleotides encoding an adenovirus tripartite leader (TPL), wherein the TPL-encoding sequence of nucleotides comprises: (a) first and second different TPL exons, wherein the

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different TPL exons are from different adenoviruses, or in a non-native order or both or (b) first, second and third same or different TPL exons, wherein at least two of the different TPL exons are from different adenoviruses, or in a non-native order or both and said TPL exons in (a) and (b) are selected from the group consisting of complete TPL exon 1, complete TPL exon 2 and complete TPL exon 3; and

(ii) said cell line supports the production of a recombinant adenovirus vector genome by complementation of a deficient viral gene in said vector genome; and

- 2) producing said adenovirus particle.

Claim 97 recites A method for producing an adenovirus particle comprising:

1) providing a packaging cell line wherein said packaging cell line comprises: a stably integrated nucleic acid molecule, comprising:

(i) a sequence of nucleotides encoding an adenovirus tripartite leader (TPL), wherein the TPL-encoding sequence of nucleotides comprises: (a) first and second different TPL exons, wherein the different TPL exons are from different adenoviruses, or in a non-native order or both or (b) first, second and third same or different TPL exons, wherein at least two of the different TPL exons are from different adenoviruses, or in a non-native order or both and said TPL exons are selected from the group consisting of complete TPL exon 1, complete TPL exon 2 and complete TPL exon 3, and

(ii) a sequence of nucleotides encoding adenovirus fiber protein;

and

- 2) producing an adenovirus particle.

Thus, all the pending claims specify that the stably integrated molecule introduced into the packaging cell genome contains a TPL sequence such that at least two of the TPL exons are from different adenoviruses or in non-native order or both, and selected from either complete TPL exon 1, complete TPL exon 2 and complete TPL exon 3, or complete TPL exon 1, partial TPL exon 1, complete TPL exon 2 and complete TPL exon 3. The claims in the '292 patent application do not specify such order. In addition, the claims in the '292 patent application are directed to methods for making fiberless a recombinant adenovirus vector genome. The instant claims do not specify the resulting genome is fiberless, but that the genome is deficient in a structural protein.

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Hence none of the instant claims anticipate the claims in the '292 application. Anticipation requires disclosure of each element as claimed. In this instance, the instant claims do not disclose a method for producing a fiberless genome but rather methods for producing genomes with a deficiency in a structural gene, which includes genes in addition to fiber, such as penton. **Therefore, the Examiner's basis for the rejection is incorrect.**

**Analysis**

As noted above, a finding of obviousness-type double patenting requires an analysis of the claims based upon the principles of claim interpretation and does not use the claims of the copending application as disclosure. The issue is whether granting of a patent on the second set of claims extends the right of exclusivity to a claimed species. The claims in the '292 application recite a method of producing an adenovirus particle in which a packaging cell line contains a stably integrated construct that complements an adenoviral fiber gene in an adenovirus vector genome deficient in the same. Dependent claims recite that the construct can further contain certain TPL leader sequences. The claims do not encompass species as claimed herein, where at least two exons of the TPL construct come from different adenoviruses or are in non-native order or both, nor is there any evidence of record that the instant packaging cell lines and methods of producing adenovirus particles using these cell lines are obvious. There is no suggestion based on the principles of claim interpretation that the claims of the '292 application suggest using a packaging cell genome that contains a TPL sequence such that at least two of the TPL exons are from different adenoviruses or in non-native order or both, and selected from either complete TPL exon 1, complete TPL exon 2 and complete TPL exon 3, or complete TPL exon 1, partial TPL exon 1, complete TPL exon 2 and complete TPL exon 3.

As noted above, double-patenting has not been found in instances in which the claims at issue do not embrace the prior patent compounds and/or the

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claims in the prior patent do not suggest any modification that would have produced the claimed compounds in the patent or application at issue. See, e.g., Ortho Pharmaceutical Corp v. Smith, 22 USPQ2d 1119 (Fed. Cir. 1992)), in which obvious-type double patenting was not found in an instance in which the claims in the patent at suit were directed to compounds that did not encompass, structurally, the compounds claimed in the prior patents, and the compounds claimed in the prior patents did not suggest a modification of those compounds to produce compounds claimed in the patent at suit.

In this instance, the claims at issue do not embrace the '292 claims (nor do the '292 claims embrace the claims at issue in this application) and the claims in the '292 application do not suggest any modification that would have led to the specifically recited constructs in the instant packaging cell lines and methods. Therefore, as between claims in the U.S. Application No. 09/795,292 and the pending claims in the instant application, obviousness-type double patenting does not exist.

**THE REJECTION OF CLAIMS 100 AND 101 UNDER 35 U.S.C. §112, SECOND PARAGRAPH**

Claims 100 and 101 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. The Office Action states that elements recited in Claim 100 are incongruous with elements recited in Claim 6, on which Claim 100 depends. Claim 101 is rejected as being dependent on Claim 100. Reconsideration and withdrawal of this rejection is respectfully requested.

Claim 100, as amended herein, is rewritten as an independent claim directed to an isolated nucleic acid molecule contained in the plasmid pCLF. Thus, an incongruity, if any, between Claim 100 and Claim 6 is rendered moot. The rejection also is rendered moot with respect to Claim 101, which depends on Claim 100.

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**THE REJECTION OF CLAIMS 9, 18, 100, 102 AND 103 UNDER 35 U.S.C.  
§112, FIRST PARAGRAPH**

Claims 9, 18, 100, 102 and 103 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to enable one of skill in the art to make and/or use the subject matter of the claims. The Office Action maintains that plasmids pCLF, pDV60, pDV67, pDV69, pDV80 and pDV90 are required elements of the claims and as such must be known and readily available to the public or be obtainable by a repeatable method set forth in the specification. The Office Action further states that a statement of deposit of the plasmids may satisfy the enablement requirement. Reconsideration and withdrawal of this rejection is respectfully requested in light of the amendments and remarks herein and in light of the interviews of November 23 and December 2.

**RELEVANT LAW**

Deposit of biological materials is not necessary if the materials, or starting materials, are known and readily available to the public, or obtainable by a repeatable method set forth in the specification. No deposit is required when simple screening and selection methods can be applied to publicly available materials to arrive at the claimed materials, and disclosure of a working example can suffice to establish screening and selection methods as not requiring undue experimentation. *Tabuchi v. Nubel* 559 F.2d 1183, 194 USPQ 521 (CCPA 1977). Factors that can be applied to determine ready availability can include commercial availability, references to the biological material in printed publications, and evidence of predictable isolation techniques. MPEP §2404.01.

**ANALYSIS**

Deposit of biological materials is not necessary if the materials, or starting materials, are known and readily available to the public, or obtainable by a repeatable method set forth in the specification. For plasmids pCLF, pDV60, pDV67, pDV69, pDV80 and pDV90, the complete nucleotide sequences are

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provided in the Sequence Listing as SEQ ID NOs. 8, 43, 44, 47, 64 and 65, respectively.

In the interviews of November 23 and December 2, the Examiner suggested that this rejection may be reconsidered and withdrawn if Applicant clearly points to passages in the specification that describe the sequences of each of these plasmids. Accordingly, provided below is a list of passages describing the sequence identifiers for each of the plasmids that are elements of the rejected claims:

**plasmid pCLF: page 60, line 20 - page 61, line 17**

**plasmids pDV60, pDV67, pDV69, pDV80, and pDV90: page 35, lines 6-10**

In addition, as discussed responsive to the previous Office Action, the specification sets forth detailed protocols for obtaining each plasmid from readily available starting materials (see Example 1, beginning on page 63 for construction of pCLF; Example 6, beginning on page 94, for construction of pDV60, pDV67 and pDV69; Example 10, beginning on page 107, for construction of pDV80; and Example 11, beginning on page 110, for construction of pDV90).

Thus, given the availability of the nucleic acid sequences, as well as detailed methods for arriving at such nucleic acid sequences, one of skill in the art can readily make and/or use the instantly claimed plasmids and a deposit is not necessary. Thus, Applicant respectfully submits that, as discussed above, deposited plasmids are not required for one of skill in the art to make and/or use the claimed subject matter.

**REJECTION OF CLAIMS 1, 2 and 11 UNDER 35 U.S.C. §102(b)**

Claims 1, 2 and 11 are rejected under 35 U.S.C. §102(b) as being anticipated by Logan *et al.* (*Proc. Natl. Acad. Sci. USA* 81:3655-3659 (1984)). The Office Action maintains that Logan *et al.* anticipates a nucleic acid molecule comprising two TPL exons from the same adenovirus in non-native order. To support this assertion, the Office Action points to the "sub 360-L1,3" construct

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set forth in Figure 1 of Logan *et al.*, which allegedly describes a TPL leader sequence containing TPL exon 1 operatively linked to TPL exon 2.

Reconsideration and withdrawal of this rejection is respectfully considered in light of the amendments and remarks herein, and in light of the interviews of November 23 and December 2.

**RELEVANT LAW**

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir. 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S., 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl. 1966). See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir. 1989), cert. denied, 110 S.Ct. 154 (1989).

"[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference.

Lindemann Maschinen-fabrik GmbH v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

**CLAIMS**

Claim 1 as amended herein is directed to an isolated nucleic acid molecule containing a sequence of nucleotides encoding an adenovirus tripartite leader (TPL), wherein the TPL-encoding sequence of nucleotides comprises: (a) first and second different TPL exons, wherein the different TPL exons are from different adenoviruses, or in a non-native order or both or (b) first, second and third same or different TPL exons, wherein at least two of the different TPL

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exons are from different adenoviruses, or in a non-native order or both; and said TPL exons in (a) and (b) are selected from the group consisting of complete TPL exon 1, complete TPL exon 2 and complete TPL exon 3. Claim 11 is directed to a plasmid that contains the nucleic acid molecule of claim 1.

Claim 2 is directed to an isolated nucleic acid molecule, containing: a sequence of nucleotides encoding an adenovirus tripartite leader (TPL) that comprises (a) first and second different TPL exons, wherein the different TPL exons are from different adenoviruses, or in a non-native order or both or (b) first, second and third same or different TPL exons, wherein at least two of the different TPL exons are from different adenoviruses, or in a non-native order or both, said TPL exons in (a) and (b) selected from the group consisting of complete TPL exon 1, partial TPL exon 1, complete TPL exon 2 and complete TPL exon 3, wherein the sequence of nucleotides encoding a TPL is operatively linked to an intron containing an RNA processing signal.

**Logan *et al.* Does Not Disclose All Elements of the Claims**

As amended pursuant to discussions with the Examiner during the interviews of November 23 and December 2, the language of Claims 1 and 2 clarifies that the limitation that the TPL exons be selected from the group consisting of complete TPL exon 1, complete TPL exon 2 and complete TPL exon 3 (for Claim 1) and the group consisting of complete TPL exon 1, partial TPL exon 1, complete TPL exon 2 and complete TPL exon 3 (for Claim 2), applies to clauses (a) and (b) of the claims. Logan *et al.* does not disclose isolated any isolated nucleic acid molecules containing a tripartite leader (TPL), sequence in which at least two exons are from different adenoviruses or in non-native order or both, and the TPL exons are selected from the group consisting of complete TPL exon 1, complete TPL exon 2 and complete TPL exon 3 (for Claim 1) or complete TPL exon 1, partial TPL exon 1, complete TPL exon 2 and complete TPL exon 3 (for Claim 2). The sub 360-L1,L3 construct of Logan *et*

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*al.* pointed to by the Examiner contains partial TPL exon 1 linked to partial TPL exon 3.

Claim 2 is further not anticipated by Logan *et al.* because the cited reference fails to disclose an intron containing an RNA processing signal. The Office Action alleges that Logan *et al.* discloses a 241-bp untranslated segment that includes the major late transcriptional control region to enhance E1A mRNA transcription. Logan *et al.* discloses the use of a 241-bp major late transcription promotor (page 3655, left column, first paragraph under Material and Methods). Claim 2 recites an RNA processing signal. Logan *et al.* discloses nothing regarding an RNA processing signal.

Because Logan *et al.* does not disclose any isolated nucleic acid molecules containing TPL leader sequences in which at least two of the TPL exons are from different adenoviruses or in non-native order or both and selected from the groups of exons as set forth in Claims 1 and 2, nor an RNA processing signal as set forth in Claim 2, therefore Logan *et al.* cannot anticipate Claim 1, Claim 11 dependent thereon, and Claim 2.

**THE REJECTION OF CLAIM 4 UNDER 35 U.S.C. §103(a)**

Claim 4 is rejected under 35 U.S.C. §103(a) as being unpatentable over Logan *et al.* in view of Hodges *et al.* (Molecular Physiology 48:905-918 (1995)). The Office Action alleges that it would have been obvious to insert the adenovirus intron 1 allegedly taught by Hodges *et al.* into the TPL construct allegedly taught by Logan *et al.*, to arrive at the claimed subject matter. Reconsideration and withdrawal of this rejection is respectfully requested in view of the amendments and remarks herein, and in view of the interviews of November 23 and December 2.

**RELEVANT LAW**

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (ACS Hosp.

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Systems, Inc. v. Montefiore Hosp., 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (Bd. App. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art." In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed subject matter, absent some teaching or suggestion supporting the combination (ACS Hosp. Systems, Inc. v. Montefiore Hosp., 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art" In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed subject matter, absent some teaching or suggestion supporting the combination (ACS Hosp. Systems, Inc. v Montefiore Hosp. 732 F.2d 1572, 1577. 221 USPQ 929, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used

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against its teacher" *W.L. Gore & Associates, Inc. v Garlock Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

**CLAIM 4**

Claim 4 is directed to the isolated nucleic acid molecule of Claim 2 (discussed above), where the intron is native adenovirus intron 1. As amended herein pursuant to the Examiner's suggestion in the interview of November 23, Claim 2 clarifies that the limitation of at least two different TPL exons from different adenoviruses or in non-native order or both, and selected from complete TPL exon 1, partial TPL exon 1, complete TPL exon 2 and complete TPL exon 3, applies to clauses (a) and (b) of the claim.

**The cited references, singly or in combination, do not result in the claimed subject matter**

*Logan et al.* is discussed above. As discussed above and in the interview of November 23, *Logan et al.* neither teaches nor suggests any isolated nucleic acid molecule containing a TPL construct having at least two exons from different adenoviruses or in non-native order or both, where the exons are selected from complete TPL exons 1, 2, and 3, and partial TPL exon 1. *Logan et al.* also does not teach or suggest a construct containing native adenovirus intron 1. Therefore, *Logan et al.* alone cannot teach or suggest the subject matter of the claims.

*Hodges et al.* teaches inhibition of RNA splicing by antisense oligonucleotides. *Hodges et al.* teaches plasmids containing adenovirus 2 major late transcription unit intron 1. *Hodges et al.* does not teach or suggest any TPL constructs, nor insertion of introns into such constructs. Therefore, *Hodges et al.* does not teach or suggest the subject matter of Claim 4. Moreover, because *Hodges et al.*, like *Logan et al.*, does not teach or suggest the TPL constructs as specified, nor insertion of introns into such constructs, *Hodges et al.* cannot cure the deficiencies of *Logan et al.*, therefore their combination does not result

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in the subject matter of Claim 4. Accordingly, the Examiner has failed to establish a *prima facie* case of obviousness.

**THE REJECTION OF CLAIMS 12, 13, 15-17, 20-23, 41, 47, 69 and 95-97  
UNDER 35 U.S.C. §103(a)**

Claims 12, 13, 15-17, 20-23, 41, 47, 69 and 95-97 are rejected under 35 U.S.C. §103(a) as being unpatentable over Logan *et al.*, or Sheay *et al.* (Biotechniques 15(5):856-862 (1993)) or Kaufman (Proc. Natl. Acad. Sci. U.S.A. 82:689-693 (1985)), in view of Curiel (U.S. Pat. No. 5,871,727) and Caravokyri *et al.* (J. Virology 69:6627-6633 (1995)). The Office Action alleges that Logan *et al.*, Sheay *et al.* and Kaufman teach adenovirus TPL sequences, Curiel teaches a plasmid encoding a chimeric fiber protein, and Caravokyri *et al.* teaches packaging cell lines containing nucleotide sequences that complement pIX-deficient adenoviruses under the control of an inducible promotor.

The Office Action concludes that it would have been obvious to one of ordinary skill in the art at the time the instant application was filed to have combined the TPL constructs allegedly taught by Logan *et al.*, Sheay *et al.* or Kaufman with the chimeric adenovirus fiber gene of Curiel *et al.* to generate a plasmid and further introduce the plasmid into a packaging cell line allegedly taught by Carvokyri *et al.*, to arrive at the claimed subject matter.

Reconsideration and withdrawal of this rejection is respectfully submitted in view of the amendments and remarks herein, and pursuant to the interview of December 2. It is respectfully submitted that this rejection is rendered moot with respect to Claim 13, which has been cancelled.

**CLAIMS**

Claim 12 is directed to an adenovirus vector packaging cell line, containing a stably integrated nucleic acid molecule, comprising an adenovirus tripartite leader (TPL) nucleotide sequence, said TPL nucleic sequence comprising (a) first and second different TPL exons or (b) first, second and third same or different TPL exons, said TPL exons selected from the group consisting

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of complete TPL exon 1, partial TPL exon 1, complete TPL exon 2 and complete TPL exon 3; and an operatively-linked promoter and a nucleic acid sequence that encodes an adenovirus structural protein, wherein the sequence of nucleotides that encodes the TPL consists essentially of a first TPL exon operatively linked to a complete second TPL exon operatively linked to a complete third TPL exon. Contrary to the characterization in the Office Action, claim 12 is not directed to an adenovirus packaging cell line comprising a stably integrated nucleic acid molecule comprising the nucleic acid of claims 6-8.

Claim 13 is directed to the cell line of claim 12, wherein said first TPL exon is a complete or partial TPL exon 1. Claim 15 is directed to the cell line of claim 12 wherein said promoter is an inducible promoter. Claim 16 is directed to the cell line of claim 12, wherein said adenovirus structural protein is adenovirus fiber protein or a chimeric protein which includes an adenovirus fiber protein tail domain. Claim 17 is directed to the cell line of claim 16, wherein said chimeric protein comprises an Ad3 head domain and an Ad5 tail domain or an Ad5 head domain and an Ad3 tail domain.

Claim 20 is directed to the cell line of claim 12, wherein said cell line is an epithelial cell line. Claim 21 is directed to the cell line of claim 12, wherein said cell line supports the production of a recombinant adenovirus vector genome by complementation of a deficient viral gene in said vector genome. Claim 22 is directed to the cell line of claim 21, wherein said cell line expresses an adenovirus early protein gene and a fiber gene. Claim 23 is directed to the cell line of claim 21, wherein deletion of a deficient viral gene is complemented by the expression of a gene under the control of an inducible promoter.

Claim 69 is directed to the packaging cell line of claim 12, wherein said cell line is selected from the group consisting of 293, A549, W163, HeLa, Vero, 211, 211A and an epithelial cell line, wherein said cell line comprises said stably integrated nucleic acid molecule.

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Claim 95 is directed to a method for producing an adenovirus particle comprising:

1) providing a packaging cell line wherein said packaging cell line comprises:

(i) a stably integrated first nucleic acid molecule operatively linked to a second nucleic acid molecule encoding an adenovirus structural protein, wherein said first nucleic acid molecule comprises the nucleic acid molecule of claim 2; and

ii) said cell line supports the production of a recombinant adenovirus vector genome by complementation of a deficient viral gene in said vector genome, and

2) producing said virus particle.

The nucleic acid molecule of claim 2 is an isolated nucleic acid molecule, comprising: a sequence of nucleotides encoding an adenovirus tripartite leader (TPL) that comprises (a) first and second different TPL exons, wherein the different TPL exons are from different adenoviruses, or in a non-native order or both or (b) first, second and third same or different TPL exons, wherein at least two of the different TPL exons are from different adenoviruses, or in a non-native order or both, said TPL exons in (a) and (b) selected from the group consisting of complete TPL exon 1, partial TPL exon 1, complete TPL exon 2 and complete TPL exon 3, wherein the sequence of nucleotides encoding a TPL is operatively linked to an intron containing an RNA processing signal.

Dependent Claims 41 and 47 specify that the first nucleic acid molecule is operatively linked to a promoter (Claim 41) or the adenovirus structural protein is adenovirus fiber protein.

Claim 96 recites a method for producing an adenovirus particle comprising:

1) providing a packaging cell line wherein said packaging cell line comprises:

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(i) a stably integrated nucleic acid molecule, comprising:  
    a sequence of nucleotides encoding an adenovirus tripartite leader (TPL), wherein the TPL-encoding sequence of nucleotides comprises: (a) first and second different TPL exons, wherein the different TPL exons are from different adenoviruses, or in a non-native order or both or (b) first, second and third same or different TPL exons, wherein at least two of the different TPL exons are from different adenoviruses, or in a non-native order or both and said TPL exons in (a) and (b) are selected from the group consisting of complete TPL exon 1, complete TPL exon 2 and complete TPL exon 3; and  
(ii) said cell line supports the production of a recombinant adenovirus vector genome by complementation of a deficient viral gene in said vector genome; and

2) producing said adenovirus particle.

Claim 97 recites A method for producing an adenovirus particle comprising:

1) providing a packaging cell line wherein said packaging cell line comprises: a stably integrated nucleic acid molecule, comprising:  
(i) a sequence of nucleotides encoding an adenovirus tripartite leader (TPL), wherein the TPL-encoding sequence of nucleotides comprises: (a) first and second different TPL exons, wherein the different TPL exons are from different adenoviruses, or in a non-native order or both or (b) first, second and third same or different TPL exons, wherein at least two of the different TPL exons are from different adenoviruses, or in a non-native order or both and said TPL exons are selected from the group consisting of complete TPL exon 1, complete TPL exon 2 and complete TPL exon 3, and

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(ii) a sequence of nucleotides encoding adenovirus fiber protein;  
and

- 2) producing an adenovirus particle.

Thus, all the claims recite the use of a construct containing TPL sequence in which at least two TPL exons are from different adenoviruses or in non-native order or both, and are selected from the group consisting of complete TPL exon 1, complete TPL exon 2 and complete TPL exon 3 or complete TPL exon 1, partial TPL exon 1, complete TPL exon 2 and complete TPL exon 3

#### Analysis

It is respectfully submitted that, as discussed during the interview of December 2, none of the cited references, singly or in any combination, teaches or suggests a packaging cell line, nor method of producing an adenovirus particle using such cell line, where the packaging cell line contains a TPL sequence operatively linked to an adenoviral structural gene and integrated into the genome of the cell line. Logan *et al.*, Kaufman and Sheay *et al.* do not teach or suggest any packaging cell lines, nor TPL sequences linked to a promoter and an adenovirus structural gene. Curiel *et al.*, directed to fiber variants to generate adenoviral vectors with altered tropism, also does not teach or suggest any packaging cell lines, nor operatively linking fiber variant genes (adenoviral structural genes) to TPL sequences. Therefore, Curiel *et al.* does not cure the deficiencies of Logan *et al.*, Sheay *et al.*, or Kaufman, singly or in any combination. Caravokyri *et al.* teaches a packaging cell line that complements an adenovirus by episomal expression of a plasmid containing polypeptide IX. Caravokyri *et al.* does not teach or suggest integrating a TPL sequence operatively linked to an adenoviral structural gene into the genome of a packaging cell line. Therefore, Caravokyri *et al.* does not cure the deficiencies of the remaining cited references.

Regardless of the above, in the interest of advancing the application to allowance, the rejected claims are amended herein, per the Examiner's

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suggestion, to incorporate the limitations of Claim 1 (96, 97), Claim 2 (Claim 95 and dependents) or allowed Claim 6 (Claim 12 and dependents). As the Examiner has acknowledged (see Final Office Action page 15 and also discussed in the interviews of November 23 and December 2), the prior art does not disclose, teach or suggest any constructs, cell lines or methods in which the constructs contain at least two different TPL exons from different adenoviruses or in non-native order or both, and where the TPL exons are selected from the group consisting of complete TPL exon 1, complete TPL exon 2 and complete TPL exon 3 or complete TPL exon 1, partial TPL exon 1, complete TPL exon 2 and complete TPL exon 3. Therefore, the rejection of the claims, all of which now specify these elements, should be withdrawn. Applicant reserves the right to file continuation application(s) directed to any unclaimed subject matter.

**THE REJECTION OF CLAIMS 98 AND 99 UNDER 35 U.S.C. §103(a)**

Claims 98 and 99 are rejected under 35 U.S.C. §103(a) as being unpatentable over Logan *et al.*, or Sheay *et al.* or Kaufman, in view of Curiel, Caravokyri *et al.*, and Branellec *et al.* (U.S. Pat. No. 6,410,011). The Office Action alleges that the teachings of Branellec *et al.* regarding a suicide gene would have been obvious to combine with the teachings of Logan *et al.*, or Sheay *et al.* or Kaufman, and Curiel and Caravokyri *et al.* as set forth above. This rejection is respectfully traversed.

**CLAIMS**

Claim 98 is directed to the method of claim 97, where the adenovirus particle comprises a genome encoding an exogenous protein. Claim 99 is directed to the method of claim 98, where the exogenous protein is selected from a group consisting of a tumor-suppressor protein, a biologically active fragment thereof that has tumor-suppressor activity, a suicide protein and a biologically active fragment thereof that has activity as a suicide protein.

**Analysis**

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### **Analysis**

As discussed above, Logan *et al.*, or Sheay *et al.* or Kaufman, and Curiel and Caravokyri *et al.*, singly or in combination, do not teach or suggest any packaging cell lines or methods using the cell lines in which the packaging cell line has a TPL sequence operatively linked to an adenoviral structural gene stably integrated into the genome of the cell line. Branellec *et al.*, directed to adenoviral vectors containing a recombinant suicide gene, does not cure these deficiencies. Therefore, the cited references, singly or in any combination, do not lead to the claimed subject matter.

Regardless of the above, this rejection is rendered moot with respect to Claims 98 and 99 as amended herein. These claims depend from Claim 97 which, as amended, specifies constructs containing at least two different TPL exons from different adenoviruses or in non-native order or both, and where the TPL exons are selected from the group consisting of complete TPL exon 1, complete TPL exon 2 and complete TPL exon 3 or complete TPL exon 1, partial TPL exon 1, complete TPL exon 2 and complete TPL exon 3. Therefore, as discussed above, it is respectfully submitted that this rejection be withdrawn.

\* \* \*

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In view of the above remarks and the amendments and remarks of record,  
reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,  
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